Diagnosing, Staging and Stratifying Patients with Malignant Uterine Disease

By

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Introduction

Cross-sectional imaging can play an important role in the pretreatment evaluation of gynecologic cancer patients. In cancer of the uterus, cross-sectional imaging offers an assessment of morphologic prognostic factors, including tumor size, depth of penetration, stage of disease, and lymph node status. Imaging should be viewed as a complementary tool rather than as competitive with the other methods of tumor evaluation (e.g., clinical or surgical assessment).

Endometrial Cancer

Clinical Background and Prognostic Factors

Endometrial carcinoma is the fourth most common cancer in women and the leading invasive malignancy in the female genital tract, with 40,880 new cases and 7,310 deaths expected in the United States in 2005 [1]. Endometrial cancer primarily presents at stage I (80% of cases), and the recommended treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Depending on prognostic factors such as depth of invasion and tumor grade, lymphadenectomy may also be indicated. The major diagnostic factors to be assessed in the preoperative evaluation of endometrial cancer are:

1) determination of the risk of lymph node metastasis in order to have skilled surgical consultation available;
2) diagnosing gross cervical invasion, which requires preoperative radiation therapy or a different treatment plan, i.e., radical hysterectomy instead of total abdominal hysterectomy;
3) detection of advanced disease.

The most important prognostic variables for uterine carcinoma are the histologic grade and the tumor stage [2], including depth of myometrial invasion and lymph node metastasis [2, 3]. In a study of 1,566 patients with adenocarcinoma of the uterus, the depth of myometrial invasion was found to be the single most important prognostic factor. In stage IA and IB disease, when the tumor is confined to the endometrium or to the superficial myometrium, the incidence of para-aortic lymph node metastases is only 3%. Conversely, in stage IC disease, when there is deep myometrial invasion, lymph node metastases occur in 6%-46% [3, 4]. The International Federation of Gynecology and Obstetrics (FIGO) staging is not accurate to assess the depth of

myometrial invasion or the presence of lymphadenopathy. Because clinical staging carries an overall understaging error of about 13%–22%, routine surgical staging is recommended by the FIGO [2]. Preoperative evaluation of prognostic factors helps in subspecialist treatment planning. In this context, the role of imaging is to depict deep myometrial invasion and the presence of lymphadenopathy, and to stage the tumor extent before treatment planning. Diagnostic imaging may also be helpful in a primarily obese, elderly population in which radiation therapy rather than surgery might be advocated as a primary treatment or as a preoperative adjuvant to surgery.

Use of Imaging in Clinical Guidelines

Transabdominal ultrasound (US) is considered unreliable in staging endometrial cancer. The use of transvaginal US has shown promise in the evaluation of myometrial invasion, with accuracy ranging from 69% to 93% for differentiating deep invasion (stage IC) from absent or superficial invasion (stages IA-IB) [5-11], and from 68% to 69% in differentiating stages IA, IB and IC from each other [12, 13]. In one study, high frequency transvaginal US showed a similar accuracy of 73% in the assessment of myometrial invasion [14].The limitations of US are suboptimal soft tissue contrast resolution (the tumor and the adjacent myometrium often have similar echogenicity), a relatively small field of view that precludes assessment of large tumors, and patient physique (patients with endometrial carcinoma are often obese and have short stature). False positive findings of myometrial invasion are due to polypoid tumors, pyometra, myomas, or focal adenomyosis mimicking myometrial invasion and myometrial atrophia [13]. False negative results occur in cases of superficial growth or microinvasion [13]. In addition, there are insufficient reports about the value of endovaginal sonography in predicting cervical extension, parametrial invasion, or lymphadenopathy. In one study, endovaginal ultrasound showed cervical involvement in only 7 of 10 patients with cervical extension [15].

Computed Tomography (CT) has been used for the evaluation of endometrial carcinoma with emphasis on the evaluation of the depth of myometrial invasion and assessment of lymph node status. Studies comparing imaging modalities in the assessment of myometrial invasion, the accuracies of CT, ultrasound and MRI are reported to be 58%-61%, 68%-69% and 88%-89%, respectively [6, 10]. One study found no significant difference between CT and ultrasound for the diagnosis of deep myometrial invasion [6]. Another study using angio-CT showed 100% correlation between the minimal thickness of intact uterine wall and the minimal thickness of the specimen [16]. The value of CT in diagnosing cervical extension is not evident, because identification of the limit between the cervix and the uterine corpus is difficult on axial images.

Magnetic resonance imaging (MRI) is significantly more accurate than US in both the evaluation of tumor extension into the cervix and myometrial invasion [6, 12-14]. A meta-analysis showed that the efficacy of contrast-enhanced MRI is significantly greater than that of US, CT, or non-contrast MRI in the evaluation of the depth of myometrial invasion in patients with endometrial cancer [17] The superiority of MRI to clinical examination and CT in staging has also been documented, and the overall staging accuracy of MRI has been reported to be between 85-93% [6, 10, 13, 18-20]. It is generally agreed that, at present, MRI provides the most accurate and consistent evaluation of patients with endometrial cancer. The assessment of the depth of myometrial invasion shows significant improvement with the use of dynamic scanning (accuracy of 55%-77% for non-contrast images versus 85%-91% for contrast-enhanced images) [21-26]. Compared with T2-weighted images, the use of contrast media will reduce both overestimation as well as underestimation of depth of myometrial invasion. The erroneous MRI

assessment of the depth of myometrial invasion can sometimes be ascribed to as large polypoid endometrial cancer, which distends the uterus so that the thin rim of myometrium is stretched over it rather than deeply infiltrated [13, 27]. Cervical extension can be diagnosed reliably with accuracy ranging from 86%-95% [22, 28, 29]. One study comparing MR imaging with fractional curettage and hysteroscopy showed that MR imaging had the highest sensitivity (91%) and specificity (96%) for the diagnosis of cervical involvement in endometrial cancer [29]. A recent meta-analysis showed that use of contrast-enhanced MRI significantly affects the post-test probability of deep myometrial invasion in patients with all grades of endometrial cancer and could be used to select patients for specialist referral [30].

Ultrasound has a significantly lower sensitivity for the detection of pelvic lymph node metastases than either CT or MRI. The efficacy of CT and MRI in the evaluation of lymph node metastases is similar, and both modalities rely on anatomic findings of nodal size (equal to or greater than 1 cm on short axis). Lymphography is not recommended for the evaluation of cancer of the endometrium.

The role of positron emission tomography (PET) in endometrial cancer imaging is still under investigation. PET was reported to be useful in post-therapy surveillance, both for the localization of suspected recurrences and for the detection of asymptomatic recurrent disease [31]. A study showed that in the detection of recurrence and the evaluation of treatment response, FDG-PET, with help from CT/MRI, performed better (sensitivity 100.0%, specificity 88.2%, and accuracy 93.3%) than combined conventional imaging (sensitivity 84.6%, specificity 85.7%, and accuracy 85.0%) and tumor markers (sensitivity 100.0%, specificity 70.6%, and accuracy 83.3%). The results of FDG-PET correlated well with the clinical outcome of the patients, with patients with negative PET results tending to show disease-free courses [32].

Recommended Imaging Approach

Ultrasound, especially with the use of endovaginal sonography, is sometimes considered to be the primary imaging approach. However, in patients in whom ultrasound is suboptimal or in whom the results of imaging studies will directly influence the choice of therapy and guide in therapy planning, the higher accuracy of contrast-enhanced MRI warrants its use. In patients presenting with a large endometrial tumor, MRI should be preferred to CT and should represent the primary imaging technique. If cervical involvement is the major clinical concern, MRI is the study of choice. However, there are no outcome or cost-effectiveness studies on imaging evaluation of endometrial cancer. PET imaging is promising in the post-treatment surveillance of endometrial cancer patients.

Conclusion

Patients with endometrial carcinoma should undergo cross-sectional imaging only in cases of clinical staging difficulties, including obese patients, patients with large tumors, poor histologic tumor grade, or possible cervical involvement. If imaging is needed, MRI is the most accurate technique and should be the primary imaging modality.

Cervical Cancer

Cervical carcinoma is the third most common gynecological malignancy in the United States, with 10,370 new cases and 3,710 deaths expected in 2005 [1]. Cervical cancer staging is based on clinical FIGO criteria [33], which include findings from physical examination, colposcopy,

lesion biopsy, conventional radiologic studies (e.g., chest radiography, intravenous urography, barium enema and lymphangiography) and endoscopic studies (e.g., cystoscopy, sigmoidoscopy) [34]. Patients with cervical cancer of FIGO stage IIA or lower can be treated with radical hysterectomy and pelvic lymphadenectomy, combined radiation-chemotherapy or in some cases radiation therapy alone,[2] while patients with cervical cancer stage IIB or higher (documented parametrial disease) are best treated by a combination of radiotherapy and chemotherapy. Although accurate cervical cancer staging is crucial for appropriate treatment selection and planning, compared to surgical staging, FIGO clinical staging has been shown to result in understaging of up to 20% to 30% in stage IB, up to 23% in stage IIB, and almost 40% in stage IIIB, as well as overstaging of approximately 64% in stage IIIB [35-39].

The greatest challenges in the clinical evaluation of patients with cervical cancer are the estimation of tumor size, especially if the tumor is primarily endocervical in location; the assessment of parametrial and pelvic sidewall invasion; and the evaluation of lymph node and distant metastases. Modern cross-sectional imaging can assist in the evaluation of these prognostic factors, and there is a body of literature showing the superiority of computed tomography (CT) and magnetic resonance imaging (MRI) to clinical staging [40-44]. The use of the conventional radiological studies recommended by the FIGO for pretreatment evaluation of cervical cancer has been declining steadily since the 1980s, and it appears that in current clinical practice, these are generally being replaced by a single cross-sectional imaging examination (either CT or MRI) providing evaluation of all morphologic prognostic factors (including tumor size, parametrial invasion, adjacent organ/tissue invasion, and lymph node metastasis) [45].

Traditionally, plain films of chest have been obtained as a staging procedure to identify pleural effusion or pulmonary metastases, which occur in the late stages of cervical cancer. However, chest CT is superior to plain films for both of these indications. Intravenous urography is a sensitive test in the detection of urinary obstruction, but a low (2.4%) incidence of urinary obstruction in stage Ib disease argues against the routine use of this test [46, 47]. Although transabdominal US can show the presence of hydronephrosis, it is limited in the evaluation of the local extent of cervical cancer. Transrectal and transvaginal US with endoluminal probes have been used in the assessment of local disease but are limited in the detection of parametrial disease and pelvic side wall involvement due to poor soft tissue contrast, small field of view and operator dependence of US [48, 49].

Reports of the accuracy of CT for cervical cancer staging range from as low as 32% to as high as 80% [41, 42, 44, 48, 50-60]. There is a consensus in the literature that the value of CT increases with higher stages of disease, and that CT has limited value (a positive predictive value of 58%) in the evaluation of early parametrial invasion [44, 54-60]. The main limitation of CT in local staging is the inadequate differentiation between tumor and normal cervical stroma or parametrial structures. Therefore, CT is mainly used in advanced disease and in the assessment of lymph nodes. CT is also performed in revealing distant metastases, planning for radiation ports, and guiding percutaneous biopsies [61].

MRI is very accurate in the determination of tumor size, tumor location (exophytic or endocervical), depth of stromal invasion, and local extension of tumor. MRI is superior to clinical evaluation in the assessment of tumor size and MRI measurements are within 0.5 cm of the surgical size in 70–90% of cases [40, 44, 62]. The staging accuracy of MRI ranges from 75%-96% [40, 56-60, 63-66]. Contrast enhancement is variable and in the assessment of local tumor invasion, T2-weighted images are superior to contrast-enhanced T1-weighted images [67].

As yet, there is no firm consensus regarding the optimal choice of cross-sectional imaging (MRI or CT). A recent meta-analysis of 57 studies (38 on MRI, 11 on CT, and 8 on MRI and CT) found that MRI was superior to CT in most aspects of staging. For example, MRI had significantly higher sensitivity than CT for parametrial invasion (74% [95% CI: 68–79%] versus 55% [95% CI: 44–66%]; $P = 0.0027$) and also for lymph node involvement (60% [95% CI: 52–68%] vs. 43% [95% CI: 37–57%; $P = 0.047$); the specificities of the two modalities were comparable to each other in evaluating both of these aspects of the disease. MRI also had higher sensitivities than CT for bladder invasion and rectal invasion [68]. However, in a recent American College of Radiology Imaging Network/Gynecologic Oncology Group (ACRIN/GOG) study, based on prospective readings from 25 academic and community imaging centers, no significant difference was found between the sensitivities of MRI (53%) and CT (42%) for advanced cervical cancer (stage IIB or higher, i.e., parametrial disease). Nevertheless, the ACRIN/GOG study did find that direct tumor visualization was significantly better on MRI than on CT (AUC 0.88 vs. 0.73; p=0.014) [33]. These results suggest that although the value of MRI and CT in current clinical practice may be roughly equivalent for staging cervical cancer, MRI is indeed a more precise staging tool than CT. In addition, MRI may be a cost-saving technique in comparison to CT, as it has been reported that patients with cervical cancer who underwent MRI as the initial study (as opposed to other diagnostic tests, including CT) required fewer tests and procedures for pretreatment evaluation [69].

Although lymphangiography was routinely used in the past for the pretreatment evaluation of lymph node metastases, it has been mostly replaced, in this role, by CT and MRI. Studies that have compared lymphangiography and CT [70-72] have shown similar accuracy (72%-91% and 71-88%, respectively) for the two modalities. CT may have a slightly higher specificity than lymphangiography (88%-95% versus 59%-93%), but lymphangiography is more sensitive than CT (63%-88% versus 53%-72%), especially in early stages (I-II) of disease [70-72]. A meta-analysis compared the utility of lymphangiography, CT and MRI in patients with cervical cancer. Although summary-receiver-operator characteristics revealed no significant differences in the overall performances of the three modalities, there was a trend toward better performance for MRI than for lymphangiography or CT [73]. The ACRIN/GOG multicenter study comparing CT, MRI and FIGO clinical staging in the pretreatment evaluation of cervical cancer found that the inclusion of CT and/or MRI findings with clinical findings substantially improved staging; nevertheless, lymph node metastases were present in 55 (32%) of 172 patients at surgical pathology despite pretreatment MRI and CT [33].

Although the role of PET in the initial evaluation of cervical cancer is still under investigation, PET can be used to assess nodal disease and tumor recurrence. In the detection of metastatic lymph nodes in patients with cervical cancer, one study reported that PET had higher sensitivity (91%) and specificity (100%) than MRI, which had a sensitivity of 73% and a specificity of 83% [74]. Another study showed that when abdominal CT is negative, PET has a sensitivity of 85.7%, a specificity of 94.4% and an accuracy of 92% for the detection of para-aortic lymph node metastasis in patients with advanced cervical cancer [75]. For the detection of recurrence, PET has been reported to have a sensitivity and specificity of 85.7%-90.3% and 76.1%-86.7%, respectively [76, 77].

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